**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Docket Number (Optional)

021167-000750US

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on May 23, 2006Signature Cortney HollandsTyped or printed
name Cortney Hollands

Application Number

10/668,778

Filed

September 22, 2003

First Named Inventor

Robert F. Balint

Art Unit

1639

Examiner

Jon D. Epperson

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Note: No more than five (5) pages may be provided.

I am the

☐

applicant/inventor.

☐

assignee of record of the entire interest.

See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒

attorney or agent of record.

Registration number 51,846☐

attorney or agent acting under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34. _____

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May 23, 2006

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒*Total of 1 forms are submitted.



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PATENT
Attorney Docket No.: 021167-000750US

On May 23, 2006

TOWNSEND and TOWNSEND and CREW LLP

By: Courtney Hollands

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Robert F. Balint, et al.

Application No.: 10/668,778

Filed: September 22, 2003

For: BREAKPOINT FUSION
FRAGMENT COMPLEMENTATION
SYSTEM

Customer No.: 20350

Confirmation No. 8095

Examiner: Jon D. Epperson

Technology Center/Art Unit: 1639

APPLICANTS' ARGUMENTS FOR PRE-
APPEAL BRIEF REVIEW - EXAMINING
GROUP 1639

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This statement is being submitted in support of the Pre-Appeal Brief Request for Review, which is submitted herewith, along with a Notice of Appeal. Applicants respectfully assert that the rejection set forth in the Office Action mailed March 9, 2006 is improper as a matter of law.

Remarks begin on page 2 of this paper.

ARGUMENTS

A. Rejections under 35 USC §103 - Obviousness

The Examiner's obviousness rejection is clearly in error because none of the cited references teach or suggest:

- (1) "an N-terminal fragment of a Class A β -lactamase protein *covalently bonded through a second Class A β -lactamase protein break-point* to a first interactor domain" and
- (2) "a C-terminal fragment of a Class A β -lactamase protein *covalently bonded through a second Class A β -lactamase protein break-point* to a second interactor domain."

See claim 63 (Emphasis added). None of the Office Actions on record cite a passage from any of the references disclosing a functional fragment complementation system having an N-terminal and C-terminal Class A β -lactamase fragments *fused through the enzyme break points* to the respective interactor domains.

Rather than pointing to a specific teaching or disclosure, the Examiner argues by negative inference that Michnick meets the above claim elements by not limiting the disclosure to specific fragment fusion constructs. See Office Action mailed March 9, 2006 at page 12, stating in part:

The Examiner disagrees. The Michnick reference is not limited to systems where the interacting pair is fused only to the 5' ends of the enzyme fragments as purported. Applicants' cited passage merely refers to a description of figure 1 outlining method steps for a *preferred embodiment* [emphasis added].

But the Examiner's negative inference rationale is based on a factually incorrect characterization of Michnick. Figure 1 is not a "preferred embodiment," as asserted by the Examiner, but is explicitly referred to within the text of Michnick as a "general description" of the system. See Michnick at Col. 4, lines 28-29 (stating "FIG. 1 shows a general description of a PCA.").

By reference to Figure 1, Michnick provides a "general description" of the PCA system in which known proteins are fused to the "5' ends of each" of the N-terminal and C-terminal fragments of the complementation protein using subcloning techniques. See Michnick at Col. 4, lines 31-33. This method results in a C-terminal fragment fused through its C-terminus to an interactor domain, rather than through its N-terminal breakpoint as set forth in Applicants' claim 63. Nowhere in Michnick is this description referred to as a "preferred embodiment" as asserted by the Examiner. In fact, this paragraph is introduced in the first sentence in reference to "[t]he present application," emphasizing the broad applicability of this "general description." See Col. 4, lines 27-28. In contrast, the very next paragraph clearly informs the reader that the description therein applies only to a "preferred embodiment." See Col. 4, lines 43-44. Obviously, the authors of Michnick knew how to limit a description to a "preferred embodiment" when they desired and intentionally did not do so for the "general description of a PCA" at Col. 4, lines 27-42. It is difficult to imagine the authors being more clear on their intention to provide a "general description" of their system.

As explained above, the "general description" of Michnick's PCA system is limited to a C-terminal fragment fused through its C-terminus to an interactor domain, rather than through its N-terminal breakpoint as set forth in Applicants' claim 63. Thus, the C-terminal fragment described in Michnick is in *exactly the opposite orientation* relative to the interactor domain when compared to Applicants' C-terminal fragment set forth in claim 63. Therefore, when the interactor domain of the C-terminal fragment binds to the interactor domain of the N-terminal fragment, the N- and C-terminal fragments in Michnick's PCA system are positioned in exactly the opposite relative orientation as compared to Applicants' claimed system. Certainly one skilled in the art would expect functional reconstitution of two enzyme fragment to be sensitive to orientation and positioning. If Michnick's system resulted in successful functional reconstitution, it cannot be fairly asserted that successful functional reconstitution would be expected with the exact opposite orientation. Indeed, why would one skilled in the art even attempt such a radical modification of Michnick's successful system? For these reasons, one skilled in the art would have no motivation to radically modify Michnick's system by providing the enzyme fragments in exactly the opposite relative orientations. And even if they were

motivated, there could be no rational expectation of achieving successful functional reconstitution.

Blau also fails to teach or suggest a functional fragment complementation system having N-terminal and C-terminal Class A β -lactamase fragments fused through the enzyme break points to the respective interactor domains. Blau describes the construction of β -galactosidase fragments in which the interactor domains (FKBP12 and FRAP) are fused through the N-termini of the β -galactosidase fragments. See page 35, lines 25-36 and Figure 2B. A similar construction is shown in Figure 7B using EGFR domains. Again, this results in exactly the opposite orientation relative to the interactor domains when compared to Applicants' fragments set forth in claim 63.

Like Blau and Michnick, Pieper does not teach or suggest fusion through an enzyme break point. In fact, Pieper fails to disclose fusion of an enzyme fragment to any interactor domain. Moreover, Pieper discloses a *uni*-molecular circularly-permuted β -lactamase, not a complementation system containing two separate oligopeptides capable of functionally reconstituting. Therefore, not only does Pieper fail to teach or suggest fusion through an enzyme break point, Pieper is wholly irrelevant to Applicants' claimed dual fragment complementation system that includes two separate peptides capable of functionally reconstituting.

Moore and Maveyraud fail to cure the defects of Blau, Michnick and Pieper as Moore and Maveyraud are merely cited for the proposition that "TEM-1 β -lactamase is a good reporter." See Official Action dated June 27, 2005 at page 12.

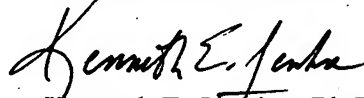
Therefore, because (1) none of the cited reference disclose a functional fragment complementation system having N-terminal and C-terminal Class A β -lactamase fragments fused through the enzyme break points to the respective interactor domains, (2) there is no motivation in the prior art to radically modify the reference systems to provide fragments having opposite orientations; and (3) there is no reasonable expectation of successfully functionally reconstituting enzyme fragments having the opposite orientation relative to the referenced systems, Applicants respectfully assert that a proper *prima facie* case of obviousness has not been set forth. See MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

B. Double Patenting Rejection

United States Patent Application No. 09/526,106 has been expressly abandoned thereby mooting the provisional double patenting rejection with respect to that application.

Claims 1, 12, and 13 of United States Patent Application No. 10/330,81 are currently non-elected as a result of the Restriction Requirement dated December 19, 2005 and the Election of Group III (claims 21-57) dated February 21, 2006, thereby mooting the provisional double patenting rejection with respect to that application.

Respectfully submitted,



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Attachments
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